U.S. National Library of Medicine
National Center for Biotechnology Information

NLM Citation: Kaur S, Christodoulou J. *MECP2* Disorders. 2001 Oct 3 [Updated 2019 Sep 19]. In: Adam MP, Ardinger HH, Pagon RA, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2020.
Bookshelf URL: https://www.ncbi.nlm.nih.gov/books/

MECP2 Disorders

Simranpreet Kaur, MSc, M Phil[1] and John Christodoulou, MBBS, PhD, FRACP, FFSc, FRCPA, FAHMS[2]

Created: October 3, 2001; Updated: September 19, 2019.

Summary

Clinical characteristics

The spectrum of *MECP2*-related phenotypes in females ranges from classic Rett syndrome to variant Rett syndrome with a broader clinical phenotype (either milder or more severe than classic Rett syndrome) to mild learning disabilities; the spectrum in males ranges from severe neonatal encephalopathy to pyramidal signs, parkinsonism, and macroorchidism (PPM-X) syndrome to severe syndromic/nonsyndromic intellectual disability.

- *Females*: Classic Rett syndrome, a progressive neurodevelopmental disorder primarily affecting girls, is characterized by apparently normal psychomotor development during the first six to 18 months of life, followed by a short period of developmental stagnation, then rapid regression in language and motor skills, followed by long-term stability. During the phase of rapid regression, repetitive, stereotypic hand movements replace purposeful hand use. Additional findings include fits of screaming and inconsolable crying, autistic features, panic-like attacks, bruxism, episodic apnea and/or hyperpnea, gait ataxia and apraxia, tremors, seizures, and acquired microcephaly.
- *Males:* Severe neonatal-onset encephalopathy, the most common phenotype in affected males, is characterized by a relentless clinical course that follows a metabolic-degenerative type of pattern, abnormal tone, involuntary movements, severe seizures, and breathing abnormalities. Death often occurs before age two years.

Diagnosis/testing

The diagnosis of a *MECP2* disorder is established by molecular genetic testing in a female proband with suggestive findings and a heterozygous *MECP2* pathogenic variant, and in a male proband with suggestive findings and a hemizygous *MECP2* pathogenic variant.

Author Affiliations: 1 Brain and Mitochondrial Research Group, Murdoch Children's Research Institute; Department of Paediatrics, University of Melbourne, Parkville, Victoria, Australia; Email: simran.kaur@mcri.edu.au. 2 Professor, Pediatrics and Biochemical, Molecular, and Human Genetics, Theme Director, Genetics Research, Murdoch Children's Research Institute; Chair of Genomic Medicine, Department of Pediatrics, University of Melbourne, Melbourne, Victoria, Australia; Email: john.christodoulou@mcri.edu.au.

Management

Treatment of manifestations: Treatment is mainly symptomatic and focuses on optimizing the individual's abilities using a multidisciplinary approach that should also include psychosocial support for family members. Risperidone may help in treating agitation; melatonin can ameliorate sleep disturbances. Treatment of seizures, constipation, gastroesophageal reflux, scoliosis, prolonged QTc, and spasticity as per standard care.

Surveillance: Periodic evaluation by the multidisciplinary team; regular assessment of QTc for evidence of prolongation; regular assessment for scoliosis.

Agents/circumstances to avoid: Drugs known to prolong the QT interval.

Genetic counseling

MECP2 disorders are inherited in an X-linked manner. More than 99% are simplex cases (i.e., a single occurrence in a family), resulting from a *de novo* pathogenic variant or possibly from inheritance of the pathogenic variant from a parent who has germline mosaicism. Rarely, a *MECP2* variant may be inherited from a heterozygous mother in whom favorable skewing of X-chromosome inactivation results in minimal to no clinical findings. When the mother is a known heterozygote, the risk to her offspring of inheriting the *MECP2* variant is 50%. When the pathogenic *MECP2* variant has been identified in the family, heterozygote testing for at-risk female relatives, prenatal testing for pregnancies at increased risk, and preimplantation genetic diagnosis are possible. Because of the possibility of parental germline mosaicism, it is appropriate to offer prenatal diagnosis to couples who have had a child with a *MECP2* disorder regardless of whether the *MECP2* pathogenic variant has been detected in a parent.

GeneReview Scope

MECP2 Disorders: Included Phenotypes [1, 2]	
Females	• *MECP2* classic Rett syndrome • Variant Rett syndrome • Mild learning disabilities
Males	• *MECP2*-related severe neonatal encephalopathy • Pyramidal signs, parkinsonism, and macroorchidism (PPM-X) syndrome • Syndromic/nonsyndromic intellectual disability

1. For other genetic causes of these phenotypes see Differential Diagnosis.
2. Note: The allelic disorder *MECP2* duplication syndrome is not included in this *GeneReview*. See Genetically Related Disorders.

Diagnosis

Note: Duplication of *MECP2* (ranging from 0.3 to 4 Mb and larger) is associated with the allelic disorder *MECP2* duplication syndrome and is not addressed in this *GeneReview*.

Suggestive Findings in Females

A *MECP2* disorder **should be suspected/considered** in females with the following clinical findings suggestive of *MECP2* classic Rett syndrome or variant Rett syndrome (based on clinical diagnostic criteria published by Neul et al [2010] [full text] prior to the widespread availability of molecular genetic testing), or mild learning disabilities.

Clinical findings of *MECP2* classic Rett syndrome and variant Rett syndrome

- Most distinguishing finding: A period of regression (range: ages 1-4 years) followed by recovery or stabilization (range: ages 2-10 years; mean: age 5 years)
- Main findings
  - Partial or complete loss of acquired purposeful hand skills
  - Partial or complete loss of acquired spoken language or language skill (e.g., babble)
  - Gait abnormalities: impaired (dyspraxic) or absence of ability
  - Stereotypic hand movements including hand wringing/squeezing, clapping/tapping, mouthing, and washing/rubbing automatisms
- Supportive findings
  - Breathing disturbances when awake
  - Bruxism when awake
  - Impaired sleep pattern
  - Abnormal muscle tone
  - Peripheral vasomotor disturbances
  - Scoliosis/kyphosis
  - Growth retardation
  - Small, cold hands and feet
  - Inappropriate laughing/screaming spells
  - Diminished response to pain
  - Intense eye communication - "eye pointing"
- Exclusionary findings
  - Brain injury secondary to peri- or postnatal trauma, neurometabolic disease, or severe infection that causes neurologic problems
  - Grossly abnormal psychomotor development in the first six months of life, with early milestones not being met

Clinical findings of *MECP2* mild learning disability. Typically mild and non-progressive. Note: Typically, females with mild learning disability are identified through molecular genetic testing following diagnosis of a first-degree relative (e.g., a more significantly affected brother or sister).

Suggestive Findings in Males

MECP2 disorders should be considered in a male with severe neonatal encephalopathy; pyramidal signs, parkinsonism, and macroorchidism (PPM-X) syndrome; or syndromic/nonsyndromic intellectual disability.

Clinical findings of *MECP2* severe neonatal encephalopathy

- Microcephaly
- Relentless clinical course that follows a metabolic-degenerative type of pattern
- Abnormal tone
- Involuntary movements
- Severe seizures
- Breathing abnormalities (including central hypoventilation or respiratory insufficiency)

Clinical findings of *MECP2* severe intellectual disability (including PPM-X syndrome)

- Moderate-to-severe intellectual disability
- Resting tremor
- Slowness of movements
- Ataxia
- PPM-X syndrome: *p*yramidal signs, *p*arkinsonism, and *m*acroorchidism

- No seizures or microcephaly
- Usually normal brain MRI, EEG, EMG, and nerve conduction velocity studies

Establishing the Diagnosis

Female proband. The diagnosis of a *MECP2* disorder **is usually established** in a female proband with suggestive findings and a heterozygous pathogenic variant in *MECP2* identified by molecular genetic testing (see Table 1).

Male proband. The diagnosis of a *MECP2* disorder **is established** in a male proband with suggestive findings and a hemizygous pathogenic variant in *MECP2* identified by molecular genetic testing (see Table 1).

Molecular genetic testing approaches can include a combination of **gene-targeted testing** (either single-gene or multigene panel) or **comprehensive genomic testing** (exome sequencing, exome array, genome sequencing) depending on the phenotype.

Gene-targeted testing requires that the clinician determine which gene(s) are likely involved, whereas genomic testing does not. Because the phenotype of *MECP2* disorders is broad, females with the distinctive findings described in Suggestive Findings are likely to be diagnosed using gene-targeted testing (see Option 1), whereas females and males with a phenotype indistinguishable from many other inherited disorders with intellectual disability and/or neonatal encephalopathy are more likely to be diagnosed using genomic testing (see Option 2).

Option 1

When the clinical findings suggest the diagnosis of a *MECP2* disorder, molecular genetic testing approaches can include use of single-gene testing or a **multigene panel**:

- **Single-gene testing.** Sequence analysis of *MECP2* detects small intragenic deletions/insertions and missense, nonsense, and splice site variants. If no pathogenic variant is found, perform gene-targeted deletion/duplication analysis to detect intragenic deletions or duplications. Note: Lack of amplification by PCR prior to sequence analysis can suggest a putative (multi)exon or whole-gene deletion on the X chromosome in affected males; confirmation requires additional testing by gene-targeted deletion/duplication analysis.

- Various **multigene panels** such as Rett/Angelman syndrome panels and more comprehensive childhood-onset epilepsy panels that include *MECP2* and other genes of interest (see Differential Diagnosis) are most likely to identify the genetic cause of the condition at the most reasonable cost while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype. Note: (1) The genes included in the panel and the diagnostic sensitivity of the testing used for each gene vary by laboratory and are likely to change over time. (2) Some multigene panels may include genes not associated with the condition discussed in this *GeneReview*. (3) In some laboratories, panel options may include a custom laboratory-designed panel and/or custom phenotype-focused exome analysis that includes genes specified by the clinician. (4) Methods used in a panel may include sequence analysis, deletion/duplication analysis, and/or other non-sequencing-based tests. For this disorder a multigene panel that also includes deletion/duplication analysis is recommended (see Table 1).

  For an introduction to multigene panels click here. More detailed information for clinicians ordering genetic tests can be found here.

Option 2

When the phenotype overlaps with many other inherited disorders characterized by intellectual disability and/or neonatal encephalopathy, **comprehensive genomic testing** (which does not require the clinician to determine which gene[s] are likely involved) is another option. **Exome sequencing** is most commonly used; **genome sequencing** is also possible.

If exome sequencing is not diagnostic, **exome array** (when clinically available) may be considered to detect (multi)exon deletions or duplications that cannot be detected by sequence analysis.

For an introduction to comprehensive genomic testing click here. More detailed information for clinicians ordering genomic testing can be found here.

Table 1. Molecular Genetic Testing Used in *MECP2* Disorders

Gene [1]	Method	Proportion of Probands with a Pathogenic Variant [2] Detectable by Method
MECP2	Sequence analysis [3, 4]	90%-95% [5]
	Gene-targeted deletion/duplication analysis [6]	5%-10% [7, 8]

1. See Table A. Genes and Databases for chromosome locus and protein.
2. See Molecular Genetics for information on allelic variants detected in this gene.
3. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Pathogenic variants may include small intragenic deletions/insertions and missense, nonsense, and splice site variants; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.
4. Lack of amplification by PCR prior to sequence analysis can suggest a putative (multi)exon or whole-gene deletion on the X chromosome in affected males; confirmation requires additional testing by gene-targeted deletion/duplication analysis.
5. Archer et al [2006], Philippe et al [2006]
6. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and a gene-targeted microarray designed to detect single-exon deletions or duplications. Gene-targeted deletion/duplication testing will detect deletions ranging from a single exon to the whole gene; however, breakpoints of large deletions and/or deletion of adjacent genes (e.g., those described by Hardwick et al [2007]) may not be detected by these methods.
7. The sizes of many reported disease-associated deletions are at the upper limits of detection by sequence analysis and the lower limits of detection by gene-targeted deletion/duplication analysis; therefore, the proportion of pathogenic variants detected by either method depends on the methods used by a laboratory.
8. Archer et al [2006], Pan et al [2006], Philippe et al [2006], Hardwick et al [2007], Zahorakova et al [2007]

Clinical Characteristics

Clinical Description

In females the spectrum of *MECP2*-related phenotypes ranges from classic Rett syndrome, to variant Rett syndrome (either milder or more severe than classic Rett syndrome), to mild learning disabilities. In males the spectrum ranges from severe neonatal encephalopathy, to pyramidal signs, parkinsonism, and macroorchidism (PPM-X) syndrome, to severe syndromic/nonsyndromic intellectual disability.

MECP2 Disorders in Females

Table 2. Features of MECP2 Disorders in Females

Phenotype	Feature	% of Persons with Feature
***MECP2* classic Rett syndrome**	Regression followed by recovery or stabilization	99%
	Deceleration of head growth	80%
	Gait abnormalities	99%
	Seizures	60%-80%
	Hand stereotypies & loss of purposeful hand skills	100% [1]
	Absence of speech; high-pitched crying	99%
	Cold extremities	99%
	Irregular breathing	99%
Variant Rett syndrome	Regression followed by recovery or stabilization	99%
	Gait abnormalities	80%-99%
	Sleep disturbences	80%-99%
	seizures	6%-80%
	Hand stereotypies & loss of purposeful hand skills	97.3%
	Breathing irregularities	80%-99%
	Agitation	80%-99%

Gold et al [2018], Einspieler & Marschik [2019], Stallworth et al [2019]
1. Stallworth et al [2019]; 44% showed different patterns including hand wringing, washing, clapping, and tapping.

***MECP2* classic Rett syndrome.** Most individuals with classic Rett syndrome are female; however, males meeting the clinical criteria for classic Rett syndrome who have a 47,XXY karyotype [Hoffbuhr et al 2001, Leonard et al 2001, Schwartzman et al 2001] and postzygotic *MECP2* variants resulting in somatic mosaicism have been described [Clayton-Smith et al 2000, Topçu et al 2002].

Although early development is reportedly normal in children with classic Rett syndrome, parents – in retrospect – often identify subtle differences compared to unaffected sibs. Most (but not all) affected children have acquired microcephaly; stereotypic hand movements and breathing irregularities are seen in the majority.

Variant Rett syndrome. Females with variant Rett syndrome exhibit a broader spectrum of clinical features than those observed in classic Rett syndrome. At the more severe end of the spectrum, development is delayed from very early infancy; congenital hypotonia and infantile spasms are also seen. At the milder end of the spectrum, regression is less dramatic and intellectual disability is much less severe; some speech may be preserved.

Mild learning disabilities. In rare instances, females with a pathogenic *MECP2* variant may only exhibit mild learning disabilities or some autistic features, presumably as a consequence of favorable skewing of X-chromosome inactivation. When there is no regression phase and no characteristic hand stereotypes, the clinical course differs from that of classic and variant Rett syndrome.

MECP2 Disorders in Males

Table 3. Features of *MECP2* Disorders in Males

Phenotype	Feature	% of Persons with Feature		
		Present	Absent	Not reported
MECP2-related severe neonatal encephalopathy [1]	Normal birth parameters	71%		29%
	Head growth deceleration / microcephaly	94%		5.8%
	Hypotonia &/or feeding difficulties in infancy	82.4%		17.6%
	Hypertonia of extremities	52.9%	11.8%	35.3%
	Movement disorder, e.g., myoclonus, tremors, & dystonia	58.8%	17.7%	23.5%
	Mild cerebral atrophy	18%	35%	47%
	Polymicrogyria	5.9%	23.5%	70.6%
	Poor head control	35%	12%	53%
	Seizures	58.8%	17.7%	23.5%
	Severe development delay	82.4%		17.6%
	Irregular breathing / sleep apnea	47.1%	29.4%	23.5%
	Gastroesophageal reflux	35.3%		64.7%
	EEG abnormality	88.2%	5.9%	5.9%
Pyramidal signs, parkinsonism, and macroorchidism (PPM-X syndrome) [2]	Psychosis	67.6%	10.8%	21.6%
	Pyramidal signs	46%	2.7%	51.3%
	Macroorchidism	19%		81%
	Intellectual disability	50%		50%
	Parkinsonism	2.7%		97.3%
	Progressive spasticity	67.6%		32.4%
	Delayed development	54%		46%
	Speech difficulties	50%		50%
	Seizures	2.7%		
	Bilateral juvenile cataract	2.7%		
	Scoliosis or kyphosis	10.8%		
	Large ears	8.1%		
	Movement disorders	32.4%		
	Apraxia	2.7%		36%
	Seizures	8.1%		91.9%
	Dysmorphic features	5.4%		94.6%

Table 3. continued from previous page.

Phenotype	Feature	% of Persons with Feature		
		Present	Absent	Not reported
Syndromic/ nonsyndromic intellectual disability [3]	Severe intellectual disability	90%		10%
	Gait abnormalities	57%	7%	36%
	Facial dysmorphism	10%	3%	87%
	Behavioral problems	40%	3%	57%
	Autistic-like behavior	3%	53%	44%
	Seizures	20%	30%	50%
	Poor/absent language skills	47%	17%	36%
	Hypotonia	23%		77%
	Microcephaly	13%	23%	64%
	History of regression	17%	27%	56%
	Spasticity	33%	17%	50%
	Sleep disturbances	13%	10%	77%

1. Schüle et al [2008]
2. Lindsay et al [1996], Claes et al [1997], Gendrot et al [1999], Orrico et al [2000], Klauck et al [2002], Winnepenninckx et al [2002], Moog et al [2003], Psoni et al [2010]
3. Lubs et al [1999], Meloni et al [2000], Orrico et al [2000], Gomot et al [2003], Meins et al [2005], Van Esch et al [2005], Ramocki et al [2009]

Severe neonatal-onset encephalopathy is characterized by a relentless clinical course that follows a metabolic-degenerative type of pattern, abnormal tone, involuntary movements, severe seizures, and breathing abnormalities (including central hypoventilation or respiratory insufficiency) [Wan et al 1999, Villard et al 2000, Zeev et al 2002, Kankirawatana et al 2006]. Often, males with a severe neonatal encephalopathy die before age two years [Schanen et al 1998, Wan et al 1999].

The severe encephalopathy phenotype appears to be rare in females [Lugtenberg et al 2009].

X-linked ID and PPM-X syndrome. PPM-X syndrome, caused by the p.(Ala140Val) *MECP2* variant in males, is characterized by moderate-to-severe intellectual disability. Most have spasticity that may be progressive; some may have extrapyramidal movements. Episodic psychosis is seen in many but not all. Most affected males also have macroorchidism. Microcephaly is variable. See also Genotype-Phenotype Correlations.

Genotype-Phenotype Correlations

Genotype-phenotype correlations are inconsistent, due in part to the pattern of X-chromosome inactivation (XCI); females who have a *MECP2* pathogenic variant and favorably skewed XCI may have mild or no manifestations [Wan et al 1999, Amir et al 2000, Cheadle et al 2000, Huppke et al 2000, Weaving et al 2003, Chae et al 2004, Schanen et al 2004,Charman et al 2005].

MECP2 pathogenic variants with some residual function that are associated with milder phenotypes include the following:

- p.(Ala140Val). The phenotype is syndromic (PPM-X) intellectual disability in males and very mild cognitive impairment in females [Dotti et al 2002, Klauck et al 2002, Gomot et al 2003, Venkateswaran et al 2014, Lambert et al 2016, Sheikh et al 2016].

- p.(Arg133Cys). The phenotype is less severe than classic Rett syndrome in females; this variant can be present in affected males [Leonard et al 2003, Sheikh et al 2016].
- p.(Arg309Cys) is found in females and males with intellectual disability and some features of *MECP2* disorders, but not classic or variant Rett syndrome [Campos et al 2007, Schönewolf-Greulich et al 2016].

Prevalence

The worldwide prevalence is 1:10,000-1:23,000 female births [Ellaway et al 1999, Armstrong et al 2010]. Reports of incidence are limited; available estimates range from 0.43-0.71:10,000 for females in France [Bienvenu et al 2006] to 0.586:10,000 for females in Serbia [Sarajlija et al 2015] and 1.09:10,000 for females in Australia [Laurvick et al 2006].

Genetically Related (Allelic) Disorders

MECP2 **duplication syndrome** is characterized in affected males by infantile hypotonia, delayed psychomotor development leading to severe intellectual disability, poor speech development, progressive spasticity, recurrent respiratory infections, and seizures.

Duplications of *MECP2* ranging from 0.3 to 4 Mb and larger are found in all affected males.

The birth prevalence of *MECP2* duplication syndrome has been reported to be 0.65:100,000 for all live births and 1:100,000 for males in Australia with the median age at diagnosis of 23.5 months [Giudice-Nairn et al 2019].

Differential Diagnosis

Table 4. Disorders to Consider in the Differential Diagnosis of *MECP2* Disorders

Differential Diagnosis Disorder	Gene(s) / Genetic Mechanism	MOI	Clinical Features of Differential Diagnosis Disorder	
			Overlapping w/*MECP2* Disorders	Distinguishing from *MECP2* Disorders
Angelman syndrome	Deficient expression or function of maternally inherited *UBE3A* allele	See footnote 1	ID, severe speech impairment, gait ataxia &/or tremulousness of the limbs; microcephaly & seizures common; DD 1st noted at age ~6 mos	In classic Rett syndrome DD is not overtly evident in the 1st 6 mos.
Early infantile epileptic encephalopathy (OMIM 300672)	*CDKL5*	XL	In females: early-onset severe seizures w/poor cognitive development; facial gestalt, cortical visual impairment; In males: severe-profound ID & early-onset intractable seizures [2]	Very early-onset seizures, facial dysmorphism, & cortical visual impairment are not generally seen in classic Rett syndrome.

Table 4. continued from previous page.

Differential Diagnosis Disorder	Gene(s) / Genetic Mechanism	MOI	Clinical Features of Differential Diagnosis Disorder	
			Overlapping w/*MECP2* Disorders	Distinguishing from *MECP2* Disorders
Rett syndrome, congenital variant (OMIM 613454)	*FOXG1*	AD	Short normal period of development before onset of regression leading to severe ID, DD, postnatal microcephaly, agenesis of the corpus callosum, seizures, dyskinesia, & hypotonia [3]	Except for microcephaly, structural abnormalities are not usually seen on brain MRI.

AD = autosomal dominant; DD = developmental delay; ID = intellectual disability; MOI = mode of inheritance; XL = X-linked
1. The risk to sibs of a proband depends on the genetic mechanism leading to the loss of *UBE3A* function: typically less than 1% risk for probands with a deletion or uniparental disomy (UPD), and as high as 50% for probands with an imprinting defect or a pathogenic variant of *UBE3A*.
2. Elia et al [2008]
3. Overlapping features and a similar facial appearance between individuals with *FOXG1* pathogenic variants has led to the suggestion that these individuals should be regarded as having *FOXG1* syndrome rather than a variant of Rett syndrome [Kortüm et al 2011].

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with a *MECP2* disorder, the evaluations summarized in Table 5 (if not performed as part of the evaluation that led to the diagnosis) are recommended.

Table 5. Recommended Evaluations Following Initial Diagnosis in Individuals with a *MECP2* Disorder

System/Concern	Evaluation	Comment
Constitutional	Measurement of height, weight, & head circumference	
Neurologic	Neurologic evaluation	To incl brain MRI; consider EEG / video monitoring if seizures are a concern.
Development	Developmental assessment	• Motor, adaptive, cognitive, & speech/language evaluation • Evaluation for early intervention / special education
Psychiatric/ Behavioral	Neuropsychiatric evaluation	In individuals age >12 mos: screening for behavior problems incl sleep disturbances, ADHD, anxiety, &/or traits suggestive of ASD
Musculoskeletal	Orthopedics, physical medicine & rehabilitation, PT, OT evaluation	To incl assessment of: • Gross motor & fine motor skills • Scoliosis • Mobility & activities of daily living & need for adaptive devices • Need for PT (to improve gross motor skills) &/or OT (to improve fine motor skills)
Gastrointestinal/ Feeding	Gastroenterology / nutrition / feeding team evaluation	To incl: • Evaluation of aspiration risk & nutritional status • History of constipation & GERD Consider need for gastric tube placement.
Respiratory	Overnight sleep studies	• Analysis for abnormalities of breathing regularity • Noninvasive assessment of pulmonary gas exchange

Table 5. continued from previous page.

System/Concern	Evaluation	Comment
Sleep disorder	Breathing monitoring using portable polygraphic screening devices	To assess occurrence of apnea & hypopnea
Cardiovascular	Cardiac evaluation	To assess for prolonged QTc
Osteopenia	Bone densitometry	To assess for osteopenia
Eyes	Ophthalmologic evaluation	To assess for reduced vision, abnormal ocular movement, strabismus
Hearing	Audiology evaluation	Assess for hearing loss
ENT/Mouth		
Genitourinary		
Integument	History & examination	Reduced perfusion of hands & feet (possible autonomic abnormalities)
Miscellaneous/ Other	Consultation w/clinical geneticist &/or genetic counselor	To incl genetic counseling
	Family supports/resources	Assess: • Use of community or online resources, e.g., Parent to Parent • Need for social work involvement for parental support • Need for home nursing referral

ADHD = attention-deficit/hyperactivity disorder; ASD = autism spectrum disorder; GERD=gastroesophageal reflux disease; OT = occupational therapy; PT = physical therapy

Treatment of Manifestations

Treatment needs to be individualized following an assessment of the affected individual's clinical problems and needs.

Management is symptomatic and focuses on optimizing the individual's abilities using a multidisciplinary approach with input from a pediatric or adult specialist physician, dietician, occupational therapist, speech therapist, music therapist, dentist, and other medical subspecialists as needed.

Table 6. Treatment of Manifestations in Individuals with a *MECP2* Disorder

Manifestation/ Concern	Treatment	Considerations/Other
DD/ID	See Developmental Delay / Intellectual Disability Management Issues.	
Epilepsy	Standardized treatment w/AEDs by an experienced neurologist	• Many AEDs may be effective; no one AED has been demonstrated effective specifically for this disorder. • Education of parents/caregivers [1]
Psychiatric/ Behavioral	Risperidone (low dose) or selective serotonin uptake inhibitors have been somewhat successful in treating agitation.	
Musculoskeletal	Scoliosis	As per guidelines [2]
Poor weight gain / failure to thrive	Feeding therapy; gastrostomy tube placement may be required for persistent feeding issues	Low threshold for clinical feeding evaluation &/or radiographic swallowing study when showing clinical signs or symptoms of dysphagia; nutritional guidelines are available. [3]

Table 6. continued from previous page.

Manifestation/ Concern	Treatment	Considerations/Other
Spasticity	Orthopedics / physical medicine & rehabilitation / PT / OT incl stretching to help avoid contractures & falls	Consider need for positioning & mobility devices, disability parking placard.
Sleep disorder	Melatonin can ameliorate sleep disturbances.	Chloral hydrate, hydroxyzine, or diphenhydramine may be used w/melatonin.
Abnormal vision &/or strabismus	Standard treatment(s) as recommended by ophthalmologist	Community vision services through early intervention or school district
Central visual impairment	No specific treatment; early intervention to help stimulate visual development	
Hearing	Hearing aids may be helpful as per otolaryngologist	Community hearing services through early intervention or school district
Gastrointestinal	• Constipation: stool softeners, prokinetics, osmotic agents, or laxatives as needed • GERD: anti-reflux agents, smaller & thickened feedings, & positioning	
Cardiovascular	Treatment for prolonged QTc	Under care of pediatric cardiologist
Osteopenia	Baseline densitometry; optimization of physical activity & calcium & vitamin D levels	Guidelines for management of bone health are available. [4]
Family/ Community	• Ensure appropriate social work involvement to connect families w/local resources, respite, & support • Care coordination to manage multiple subspecialty appointments, equipment, medications, & supplies	• Ongoing assessment for need of palliative care involvement &/or home nursing • Consider involvement in adaptive sports or Special Olympics.

AED = antiepileptic drug; DD = developmental delay; GERD = gastroesophageal reflux disease; ID = intellectual disability
1. Education of parents/caregivers regarding common seizure presentations is appropriate. For information on non-medical interventions and coping strategies for children diagnosed with epilepsy, see Epilepsy & My Child Toolkit.
2. Downs et al [2009]
3. Leonard et al [2013]
4. Jefferson et al [2016]

Developmental Disability / Intellectual Disability Management Issues

The following information represents typical management recommendations for individuals with developmental delay / intellectual disability in the United States; standard recommendations may vary from country to country.

Ages 0-3 years. Referral to an early intervention program is recommended for access to occupational, physical, speech, and feeding therapy as well as infant mental health services, special educators, and sensory impairment specialists. In the US, early intervention is a federally funded program available in all states that provides in-home services to target individual therapy needs.

Ages 3-5 years. In the US, developmental preschool through the local public school district is recommended. Before placement, an evaluation is made to determine needed services and therapies and an individualized education plan (IEP) is developed for those who qualify based on established motor, language, social, or cognitive delay. The early intervention program typically assists with this transition. Developmental preschool is center based; for children too medically unstable to attend, home-based services are provided.

All ages. Consultation with a developmental pediatrician is recommended to ensure the involvement of appropriate community, state, and educational agencies and to support parents in maximizing quality of life. Some issues to consider:

- Individualized education plan (IEP) services:
  - An IEP provides specially designed instruction and related services to children who qualify.
  - IEP services will be reviewed annually to determine if any changes are needed.
  - As required by special education law, children should be in the least restrictive environment feasible at school and included in general education as much as possible and when appropriate.
  - Vision and hearing consultants should be a part of the child's IEP team to support access to academic material.
  - PT, OT, and speech services will be provided in the IEP to the extent that the need affects the child's access to academic material. Beyond that, private supportive therapies based on the affected individual's needs may be considered. Specific recommendations regarding type of therapy can be made by a developmental pediatrician.
  - As a child enters teen years, a transition plan should be discussed and incorporated in the IEP. For those receiving IEP services, the public school district is required to provide services until age 21.
- A 504 plan (Section 504: a US federal statute that prohibits discrimination based on disability) can be considered for those who require accommodations or modifications such as front-of-class seating, assistive technology devices, classroom scribes, extra time between classes, modified assignments, and enlarged text.
- Developmental Disabilities Administration (DDA) enrollment is recommended. DDA is a public agency that provides services and support to qualified individuals. Eligibility differs by state but is typically determined by diagnosis and/or associated cognitive/adaptive disabilities.
- Families with limited income and resources may also qualify for supplemental security income (SSI) for their child with a disability.

Motor Dysfunction

Gross motor dysfunction

- Physical therapy is recommended to maximize mobility and to reduce the risk for later-onset orthopedic complications (e.g., contractures, scoliosis, hip dislocation).
- Consider use of durable medical equipment and positioning devices as needed (e.g., wheelchairs, walkers, bath chairs, orthotics, adaptive strollers).
- For muscle tone abnormalities including hypertonia or dystonia, consider involving appropriate specialists to aid in management of baclofen, tizanidine, Botox®, anti-parkinsonian medications, or orthopedic procedures.

Fine motor dysfunction. Occupational therapy is recommended for difficulty with fine motor skills that affect adaptive function such as feeding, grooming, dressing, and writing.

Oral motor dysfunction should be assessed at each visit and clinical feeding evaluations and/or radiographic swallowing studies should be obtained for choking/gagging during feeds, poor weight gain, frequent respiratory illnesses, or feeding refusal that is not otherwise explained. Assuming that the child is safe to eat by mouth, feeding therapy (typically by an occupational or speech therapist) is recommended to improve coordination or sensory-related feeding issues. Feeds can be thickened or chilled for safety. When feeding dysfunction is severe, an NG-tube or G-tube may be necessary.

Communication issues. Consider evaluation for alternative means of communication (e.g., Augmentative and Alternative Communication [AAC]) for individuals who have expressive language difficulties. An AAC evaluation can be completed by a speech-language pathologist who has expertise in the area. The evaluation will consider cognitive abilities and sensory impairments to determine the most appropriate form of communication. AAC devices can range from low-tech, such as picture exchange communication, to high-tech, such as voice-generating devices. Contrary to popular belief, AAC devices do not hinder verbal development of speech and in many cases can improve it.

Social/Behavioral Concerns

Children may qualify for and benefit from interventions used in treatment of autism spectrum disorder, including applied behavior analysis (ABA). ABA therapy is targeted to the individual child's behavioral, social, and adaptive strengths and weaknesses and typically performed one on one with a board-certified behavior analyst.

Consultation with a developmental pediatrician may be helpful in guiding parents through appropriate behavior management strategies or providing prescription medications, such as medication used to treat attention-deficit/ hyperactivity disorder (ADHD), when necessary.

Concerns about serious aggressive or destructive behavior can be addressed by a pediatric psychiatrist.

Surveillance

Many of the clinical features in females with atypical Rett syndrome (Table 2) evolve with age and hence should be reassessed every six to 12 months.

Table 7. Recommended Surveillance for Individuals with a *MECP2* Disorder

System/Concern	Evaluation	Frequency
Feeding	Measurement of growth parameters	At each multidisciplinary clinic visit; minimum annually
	Evaluation of nutritional status & safety of oral intake	
Gastrointestinal	Monitor for constipation.	
Respiratory	Monitor for evidence of aspiration, respiratory insufficiency.	
Neurologic	Monitor those w/seizures as clinically indicated.	
	Assess for new manifestations, e.g., seizures, changes in tone, movement disorders.	
Development	Monitor developmental progress & educational needs.	
Speech & language	Monitor communication skills.	
Psychiatric/ Behavioral	Behavioral assessment for anxiety, attention, & aggressive or self-injurious behavior	
Musculoskeletal	Physical medicine, OT/PT assessment of mobility, self-help skills	
	Monitor scoliosis.	
Cardiovascular	Monitor for prolonged QTc.	
Respiratory	Apnea/hyperventilation	
Miscellaneous/ Other	Assess family need for social work support (e.g., palliative/respite care, home nursing; other local resources) & care coordination.	

Agents/Circumstances to Avoid

Because individuals with *MECP2* disorders are at increased risk for life-threatening arrhythmias associated with a prolonged QT interval, avoidance of drugs known to prolong the QT interval, including the following, is recommended:

- Prokinetic agents (e.g., cisapride)

- Antipsychotics (e.g., thioridazine), tricyclic antidepressants (e.g., imipramine)
- Antiarrhythmics (e.g., quinidine, sotolol, amiodarone)
- Anesthetic agents (e.g., thiopental, succinylcholine)
- Antibiotics (e.g., erythromycin, ketoconazole)

Click here (pdf) for a more extensive list of drugs to avoid.

Evaluation of Relatives at Risk

See Genetic Counseling for issues related to testing of at-risk relatives for genetic counseling purposes.

Therapies Under Investigation

A number of clinical trials are currently under way, including observational studies, studies focused on improvement of language and communication skills, and drug trials.

For details see www.rettsyndrome.org.

Search ClinicalTrials.gov in the US and EU Clinical Trials Register in Europe for access to information on clinical studies for a wide range of diseases and conditions.

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, inheritance, and implications of genetic disorders to help them make informed medical and personal decisions. The following section deals with genetic risk assessment and the use of family history and genetic testing to clarify genetic status for family members. This section is not meant to address all personal, cultural, or ethical issues that individuals may face or to substitute for consultation with a genetics professional. —ED.

Mode of Inheritance

MECP2 disorders are inherited in an X-linked manner.

Risk to Family Members

Parents of a proband

- Approximately 99.5% of affected individuals represent simplex cases (i.e., a single occurrence in the family).
- Female proband. *MECP2* molecular genetic testing is recommended for both parents.
- Male proband. *MECP2* molecular genetic testing is recommended for the mother. (Note: The father of an affected male will not have a *MECP2* disorder nor will he be hemizygous for the *MECP2* pathogenic variant; therefore, he does not require further evaluation/testing.)
- The mother of a proband who is found to be heterozygous for a *MECP2* variant may have favorably skewed X-chromosome inactivation that results in her being unaffected or mildly affected.
- If the *MECP2* pathogenic variant found in the proband cannot be detected in the leukocyte DNA of either parent, possible explanations include a *de novo* pathogenic variant in the proband or germline mosaicism in a parent. Maternal and paternal germline mosaicism have been reported [Amir et al 1999, Zeev et al 2002, Mari et al 2005].
    - Maternal germline mosaicism was reported in one of nine pregnancies [Mari et al 2005, Venâncio et al 2007].
    - Paternal germline mosaicism was reported in five fathers of affected daugthers from 21 families [Zhang et al 2019].

Sibs of a proband. The risk to sibs depends on the genetic status of the parents:

- If the mother of the proband has a *MECP2* pathogenic variant, the chance of transmitting it in each pregnancy is 50%.
    - Females who inherit the pathogenic variant are at high risk of developing a *MECP2* disorder, although skewed X-chromosome inactivation may result in a variable phenotype.
    - Males who inherit the variant may have a severe neonatal encephalopathy or, if they survive the first year, will most likely have a severe intellectual disability syndrome.
- If the proband represents a simplex case (i.e., a single occurrence in a family) and if the *MECP2* pathogenic variant cannot be detected in the leukocyte DNA of either parent, the risk to sibs is greater than that of the general population because of the possibility of parental germline mosaicism [Amir et al 1999, Zeev et al 2002, Mari et al 2005, Venâncio et al 2007, Zhang et al 2019].

Offspring of a proband

- Each child of a female proband with a *MECP2* disorder has a 50% chance of inheriting the *MECP2* pathogenic variant. Females with more severe *MECP2* disorders do not reproduce; mildly affected females have reproduced.
- Males with a *MECP2* disorder are not known to reproduce.

Other family members. The risk to other family members depends on the genetic status of the proband's mother: if the mother is affected or has a pathogenic *MECP2* variant, her family members may be at risk.

Related Genetic Counseling Issues

First-degree female relatives. Once the pathogenic *MECP2* variant has been identified in a proband, it is appropriate to offer testing to all first-degree female relatives regardless of their clinical status. Apparently unaffected sisters of a female proband with a *MECP2* disorder may be heterozygous for the *MECP2* variant present in their sister but have few to no manifestations because of skewed X-chromosome inactivation. Genetic counseling should address this possibility as clinically unaffected sisters may be at risk of transmitting the pathogenic *MECP2* variant to their children.

Family planning

- The optimal time for determination of genetic risk and discussion of the availability of prenatal testing is before pregnancy.
- It is appropriate to offer genetic counseling (including discussion of potential risks to offspring and reproductive options) to young adults who are mildly affected or are at risk of having a pathogenic *MECP2* variant.

DNA banking is the storage of DNA (typically extracted from white blood cells) for possible future use. Because it is likely that testing methodology and our understanding of genes, allelic variants, and diseases will improve in the future, consideration should be given to banking DNA of affected individuals.

Prenatal Testing and Preimplantation Genetic Diagnosis

Once the *MECP2* pathogenic variant has been identified in an affected family member, prenatal testing for a pregnancy at increased risk and preimplantation genetic diagnosis are possible. Males with a *MECP2* variant who survive infancy will most likely have severe intellectual disability. The phenotype in a female with a *MECP2* variant is difficult to predict and can range from apparently normal to severely affected.

Note: Because parental germline mosaicism for a *MECP2* pathogenic variant has been reported in multiple families, it is appropriate to offer prenatal testing to the parents of a child with a *MECP2* disorder whether or not the *MECP2* pathogenic variant has been identified in the leukocyte DNA of either parent.

Resources

GeneReviews staff has selected the following disease-specific and/or umbrella support organizations and/or registries for the benefit of individuals with this disorder and their families. GeneReviews is not responsible for the information provided by other organizations. For information on selection criteria, click here.

- **International Rett Syndrome Foundation (IRSF)**
  4600 Devitt Drive
  Cincinnati OH 45246
  Phone: 800-818-7388 (toll-free); 513-874-3020
  Fax: 513-874-2520
  www.rettsyndrome.org
- **My46 Trait Profile**
  Rett syndrome
- **National Library of Medicine Genetics Home Reference**
  Rett syndrome
- **NCBI Genes and Disease**
  Rett syndrome
- **Rett New Zealand**
  PO Box 28 049
  Wellington
  New Zealand
  Phone: 04 475 9265
  Email: rett.info@nzord.org.nz
  www.rettsyndrome.org.nz
- **Rett Syndrome Europe**
  www.rettsyndrome.eu
- **Medical Home Portal**
  The Parents & Families section of the Medical Home Portal provides information and resources to help families learn how to better care for a child with chronic and complex conditions and to become more effective partners in their child's care.
  Department of Pediatrics University of Utah
  P.O. Box 581289
  Salt Lake City UT 84158
  Phone: 801-213-3920
  Email: info@medicalhomeportal.org

For Parents & Families

- **Rett Syndrome Research Trust**
  67 Under Cliff Road
  Trumbull CT 06611
  Phone: 203-445-0041
  Email: info@rsrt.org
  reverserett.org
- **Rett UK**
  Langham House West
  Mill Street
  Luton LU1 2NA
  United Kingdom
  Phone: 01582 798 910
  Email: info@rettuk.org
  www.rettuk.org
- **Australian Rett Syndrome Study / InterRett Registry**
  Telethon Institute for Child Health Research
  PO Box 855
  West Perth 6872
  Australia
  Phone: +61 8 9489 7790; +61 419 956 946
  Fax: +61 8 9489 7700
  Email: rett@ichr.uwa.edu.au
  www.aussierett.org.au/about-us.aspx

Molecular Genetics

Information in the Molecular Genetics and OMIM tables may differ from that elsewhere in the GeneReview: tables may contain more recent information. —ED.

Table A. MECP2 Disorders: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
MECP2	Xq28	Methyl-CpG-binding protein 2	MECP2 @ LOVD CCHMC - Human Genetics Mutation Database (MECP2) RettBASE	MECP2	MECP2

Data are compiled from the following standard references: gene from HGNC; chromosome locus from OMIM; protein from UniProt. For a description of databases (Locus Specific, HGMD, ClinVar) to which links are provided, click here.

Table B. OMIM Entries for MECP2 Disorders (View All in OMIM)

300005	METHYL-CpG-BINDING PROTEIN 2; MECP2

Table B. continued from previous page.

300055	MENTAL RETARDATION, X-LINKED, SYNDROMIC 13; MRXS13
300496	AUTISM, SUSCEPTIBILITY TO, X-LINKED 3; AUTSX3
300673	ENCEPHALOPATHY, NEONATAL SEVERE, DUE TO MECP2 MUTATIONS
312750	RETT SYNDROME; RTT

Molecular Pathogenesis

Loss of the protein MeCP2 leads to epigenetic aberrations of chromatin, suggesting that MeCP2 deficiency could lead to loss of imprinting, thereby contributing to the pathogenesis of Rett syndrome [Horike et al 2005, Kaufmann et al 2005, Makedonski et al 2005].

The nuclear MeCP2 protein functional domains include:

- Methyl binding domain (MBD): binds specifically to DNA at symmetrically methylated CpGs within chromatin [Hansen et al 2010, Casas-Delucchi et al 2012]
- Transcription repression domain (TRD): responsible for recruiting other proteins that mediate transcription repression
- A-T hook domain: basic residues that bind A-T rich DNA [Baker et al 2013, Heckman et al 2014]
- WW domain: conserved C-terminal domain [Buschdorf & Stratling 2004]

It has also been shown that MeCP2 plays a role in gene splicing [Young et al 2005] and in long-range chromatin remodeling [Horike et al 2005], and may be a transcriptional activator [Chahrour et al 2008].

Mechanism of disease causation. Most pathogenic *MECP2* variants occur *de novo*. It has been suggested that pathogenic variants result in loss of protein function; some functional studies show that pathogenic *MECP2* variants affect the MBD or TRD domains of the abnormal protein, depending on the location of the variant [Kudo et al 2001, Kudo et al 2002, Kudo et al 2003].

***MECP2*-specific laboratory technical considerations.** Two transcripts have been described:

- NM_001110792.1: encodes *MECP2_e1*, includes exons 1, 3, and 4 but not exon 2 (498 amino acids)
- NM_004992.3, encodes *MECP2_e2,* includes exons 2, 3, and 4 but not exon 1 (486 amino acids)

Although the isoforms are nearly identical, use of two alternative start codons creates alternative N-termini. The e1 transcript is much more highly expressed in brain than the e2 transcript [Kriaucionis & Bird 2004, Mnatzakanian et al 2004].Of note:

- Exon 1 (*MECP2_e1)*: pathogenic variants in exon 1 are rare and include variants in the start codon (p.Met1?) and p.Ala2 as well as variant frameshift changes [Amir et al 2005, Evans et al 2005, Poirier et al 2005, Ravn et al 2005, Saxena et al 2006, Saunders et al 2009, Sheikh et al 2017].
- Exon 2 (*MECP2_e2*): a pathogenic variant in the start codon (p.Met1?) has been reported in exon 2 [Gauthier et al 2005].

The majority of pathogenic variants occur in the region encoding the methyl binding domain (MBD, exons 3 and 4; amino acids 90-174 of the MeCP2 e2 isoform), affecting the ability of the MeCP2 protein to bind to target DNA. A number of highly recurrent nonsense variants are found in the transcriptional repression domain (TRD, exon 4; amino acids 219-322 of the MeCP2 e2 isoform) and beyond the TRD, a large number of frameshift variants delete the C-terminal end of the protein (3' end of exon 4).

Table 8. Notable *MECP2* Pathogenic Variants

Reference Sequences	DNA Nucleotide Change	Predicted Protein Change	Comment [Reference]
NM_004492.3 NP_004983.1	c.473C>T	p.(Thr158Met)	Common, recurrent pathogenic variants [Miltenberger-Miltenyi & Laccone 2003, Archer et al 2006, Philippe et al 2006]
	c.502C>T	p.(Arg168Ter)	
	c.763C>T	p.(Arg255Ter)	
	c.808C>T	p.(Arg270Ter)	
	c.916C>T	p.(Arg306Cys)	
	c.397C>T	p.(Arg133Cys)	Milder phenotype in females is consistent w/in vitro functional studies showing that DNA binding is not impaired [Leonard et al 2003, Sheikh et al 2016].
	c.419C>T	p.(Ala140Val)	Non-classic, variant Rett syndrome, observed in familial cases w/affected males [Dotti et al 2002, Klauck et al 2002, Gomot et al 2003, Venkateswaran et al 2014, Lambert et al 2016, Sheikh et al 2016]; heterozygous females may have mild ID & impaired speech acquistion [Klauck et al 2002, Lambert et al 2016].
	c.925C>T	p.(Arg309Trp)	Observed in females & males w/ID & some features of a *MECP2* disorder, but not classic or variant Rett syndrome [Campos et al 2007, Schönewolf-Greulich et al 2016]

ID = intellectual disability
Variants listed in the table have been provided by the authors. *GeneReviews* staff have not independently verified the classification of variants.
GeneReviews follows the standard naming conventions of the Human Genome Variation Society (varnomen.hgvs.org). See Quick Reference for an explanation of nomenclature.

References

Published Guidelines / Consensus Statements

Downs J, Bergman A, Carter P, Anderson A, Palmer GM, Roye D, van Bosse H, Bebbington A, Larsson EL, Smith BG, Baikie G, Fyfe S, Leonard H. Guidelines for management of scoliosis in Rett syndrome patients based on expert consensus and clinical evidence. Spine. 2009;34:E607–17. PubMed PMID: 19644320.

Literature Cited

Amir RE, Fang P, Yu Z, Glaze DG, Percy AK, Zoghbi HY, Roa BB, Van den Veyver IB. Mutations in exon 1 of MECP2 are a rare cause of Rett syndrome. J Med Genet. 2005;42:e15. PubMed PMID: 15689438.

Amir RE, Van den Veyver IB, Schultz R, Malicki DM, Tran CQ, Dahle EJ, Philippi A, Timar L, Percy AK, Motil KJ, Lichtarge O, Smith EO, Glaze DG, Zoghbi HY. Influence of mutation type and X chromosome inactivation on Rett syndrome phenotypes. Ann Neurol. 2000;47:670–9. PubMed PMID: 10805343.

Amir RE, Van den Veyver IB, Wan M, Tran CQ, Francke U, Zoghbi HY. Rett syndrome is caused by mutations in X-linked MECP2, encoding methyl- CpG-binding protein 2. Nat Genet. 1999;23:185–8. PubMed PMID: 10508514.

Archer HL, Whatley SD, Evans JC, Ravine D, Huppke P, Kerr A, Bunyan D, Kerr B, Sweeney E, Davies SJ, Reardon W, Horn J, MacDermot KD, Smith RA, Magee A, Donaldson A, Crow Y, Hermon G, Miedzybrodzka Z, Cooper DN, Lazarou L, Butler R, Sampson J, Pilz DT, Laccone F, Clarke AJ. Gross rearrangements of the MECP2 gene are found in both classical and atypical Rett syndrome patients. J Med Genet. 2006;43:451–6. PubMed PMID: 16183801.

Armstrong AH, Hangauer J, Agazzi H, Nunez A, Gieron-Korthals M. Individuals with intellectual and developmental disabilities. In: David AS, ed. *Handbook of Pediatric Neuropsychology*. New York: Springer. 2010;537-50.

Baker SA, Chen L, Wilkins AD, Yu P, Lichtarge O, Zoghbi HY. An AT-hook domain in MeCP2 determines the clinical course of Rett syndrome and related disorders. Cell. 2013;152:984–96. PubMed PMID: 23452848.

Bienvenu T, Philippe C, de Roux N, Raynaud M, Bonnefond JP, Pasquier L, Lesca G, Mancini J, Jonveaux P, Moncla A, Feingold J, Chelly J, Villard L. The incidence of Rett syndrome in France. Pediatr Neurol. 2006;34:372–5. PubMed PMID: 16647997.

Buschdorf JP, Stratling WH. A WW domain binding region in methyl-CpG-binding protein MeCP2: impact on Rett syndrome. J Mol Med. 2004;82:135–43. PubMed PMID: 14618241.

Campos M Jr, Abdalla CB, Santos-Rebouças CB, dos Santos AV, Pestana CP, Domingues ML, dos Santos JM, Pimentel MM. Low significance of MECP2 mutations as a cause of mental retardation in Brazilian males. Brain Dev. 2007;29:293–7. PubMed PMID: 17084570.

Casas-Delucchi CS, Becker A, Bolius JJ, Cristina Cardoso M. Targeted manipulation of heterochromatin rescues MeCP2 Rett mutants and re-establishes higher order chromatin organization. Nucl Acids Res. 2012;40:e176. PubMed PMID: 22923521.

Chae JH, Hwang H, Hwang YS, Cheong HJ, Kim KJ. Influence of MECP2 gene mutation and X-chromosome inactivation on the Rett syndrome phenotype. J Child Neurol. 2004;19:503–8. PubMed PMID: 15526954.

Chahrour M, Jung SY, Shaw C, Zhou X, Wong ST, Qin J, Zoghbi HY. MeCP2, a key contributor to neurological disease, activates and represses transcription. Science. 2008;320:1224–9. PubMed PMID: 18511691.

Charman T, Neilson TC, Mash V, Archer H, Gardiner MT, Knudsen GP, McDonnell A, Perry J, Whatley SD, Bunyan DJ, Ravn K, Mount RH, Hastings RP, Hulten M, Orstavik KH, Reilly S, Cass H, Clarke A, Kerr AM, Bailey ME. Dimensional phenotypic analysis and functional categorisation of mutations reveal novel genotype-phenotype associations in Rett syndrome. Eur J Hum Genet. 2005;13:1121–30. PubMed PMID: 16077736.

Cheadle JP, Gill H, Fleming N, Maynard J, Kerr A, Leonard H, Krawczak M, Cooper DN, Lynch S, Thomas N, Hughes H, Hulten M, Ravine D, Sampson JR, Clarke A. Long-read sequence analysis of the MECP2 gene in Rett syndrome patients: correlation of disease severity with mutation type and location. Hum Mol Genet. 2000;9:1119–29. PubMed PMID: 10767337.

Claes S, Devriendt K, D'Adamo P, Meireleire J, Raeymaekers P, Toniolo D, Cassiman JJ, Fryns JP. X-linked severe mental retardation and a progressive neurological disorder in a Belgian family: clinical and genetic studies. Clin Genet. 1997;52:155–61. PubMed PMID: 9377804.

Clayton-Smith J, Watson P, Ramsden S, Black GC. Somatic mutation in MECP2 as a non-fatal neurodevelopmental disorder in males. Lancet. 2000;356:830–2. PubMed PMID: 11022934.

Dotti MT, Orrico A, De Stefano N, Battisti C, Sicurelli F, Severi S, Lam CW, Galli L, Sorrentino V, Federico A. A Rett syndrome MECP2 mutation that causes mental retardation in men. Neurology. 2002;58:226–30. PubMed PMID: 11805248.

Downs J, Bergman A, Carter P, Anderson A, Palmer GM, Roye D, van Bosse H, Bebbington A, Larsson EL, Smith BG, Baikie G, Fyfe S, Leonard H. Guidelines for management of scoliosis in Rett syndrome patients based on expert consensus and clinical evidence. Spine. 2009;34:E607–17. PubMed PMID: 19644320.

Einspieler C, Marschik PB. Regression in Rett syndrome: developmental pathways to its onset. Neurosci Biobehav Rev. 2019;98:320–32. PubMed PMID: 30832924.

Elia M, Falco M, Ferri R, Spalletta A, Bottitta M, Calabrese G, Carotenuto M, Musumeci SA, Lo Giudice M, Fichera M. CDKL5 mutations in boys with severe encephalopathy and early-onset intractable epilepsy. Neurology. 2008;71:997–9. PubMed PMID: 18809835.

Ellaway C, Williams K, Leonard H, Higgins G, Wilcken B, Christodoulou J. Rett syndrome: randomized controlled trial of L-carnitine. J Child Neurol. 1999;14:162–7. PubMed PMID: 10190267.

Evans JC, Archer HL, Whatley SD, Kerr A, Clarke A, Butler R. Variation in exon 1 coding region and promoter of MECP2 in Rett syndrome and controls. Eur J Hum Genet. 2005;13:124–6. PubMed PMID: 15367913.

Gauthier J, de Amorim G, Mnatzakanian GN, Saunders C, Vincent JB, Toupin S, Kauffman D, St-Onge J, Laurent S, Macleod PM, Minassian BA, Rouleau GA. Clinical stringency greatly improves mutation detection in Rett syndrome. Can J Neurol Sci. 2005;32:321–6. PubMed PMID: 16225173.

Gendrot C, Ronce N, Raynaud M, Ayrault AD, Dourlens J, Castelnau P, Muh JP, Chelly J, Moraine C. X-linked nonspecific mental retardation (MRX16) mapping to distal Xq2 8: linkage study and neuropsychological data in a large family. Am J Med Genet. 1999;83:411–8. PubMed PMID: 10232754.

Giudice-Nairn P, Downs J, Wong K, Wilson D, Ta D, Gattas M, Amor D, Thompson E, Kirrali-Borri C, Ellaway C, Leonard H. The incidence, prevalence and clinical features of MECP2 duplication syndrome in Australian children. J Paediatr Child Health. 2019. Epub ahead of print. PubMed PMID: 30756435.

Gold WA, Krishnaraj R, Ellaway C, Christodoulou J. Rett syndrome: a genetic update and clinical review focusing on comorbidities. ACS Chem Neurosci. 2018;9:167–76. PubMed PMID: 29185709.

Gomot M, Gendrot C, Verloes A, Raynaud M, David A, Yntema HG, Dessay S, Kalscheuer V, Frints S, Couvert P, Briault S, Blesson S, Toutain A, Chelly J, Desportes V, Moraine C. MECP2 gene mutations in non-syndromic X-linked mental retardation: phenotype-genotype correlation. Am J Med Genet A. 2003;123A:129–39. PubMed PMID: 14598336.

Hansen JC, Ghosh RP, Woodcock CL. Binding of the Rett syndrome protein, MeCP2, to methylated and unmethylated DNA and chromatin. IUBMB Life. 2010;62:732–8. PubMed PMID: 21031501.

Hardwick SA, Reuter K, Williamson SL, Vasudevan V, Donald J, Slater K, Bennetts B, Bebbington A, Leonard H, Williams SR, Smith RL, Cloosterman D, Christodoulou J. Delineation of large deletions of the MECP2 gene in Rett syndrome patients, including a familial case with a male proband. Eur J Hum Genet. 2007;15:1218–29. PubMed PMID: 17712354.

Heckman LD, Chahrour MH, Zoghbi HY. Rett-causing mutations reveal two domains critical for MeCP2 function and for toxicity in MECP2 duplication syndrome mice. eLife. 2014;3:e02676. PubMed PMID: 24970834.

Hoffbuhr K, Devaney JM, LaFleur B, Sirianni N, Scacheri C, Giron J, Schuette J, Innis J, Marino M, Philippart M, Narayanan V, Umansky R, Kronn D, Hoffman EP, Naidu S. MeCP2 mutations in children with and without the phenotype of Rett syndrome. Neurology. 2001;56:1486–95. PubMed PMID: 11402105.

Horike S, Cai S, Miyano M, Cheng JF, Kohwi-Shigematsu T. Loss of silent-chromatin looping and impaired imprinting of DLX5 in Rett syndrome. Nat Genet. 2005;37:31–40. PubMed PMID: 15608638.

Huppke P, Laccone F, Kramer N, Engel W, Hanefeld F. Rett syndrome: analysis of MECP2 and clinical characterization of 31 patients. Hum Mol Genet. 2000;9:1369–75. PubMed PMID: 10814718.

Jefferson A, Leonard H, Siafarikas A, Woodhead H, Fyfe S, Ward LM, Munns C, Motil K, Tarquinio D, Shapiro JR, Brismar T, Ben-Zeev B, Bisgaard AM, Coppola G, Ellaway C, Freilinger M, Geerts S, Humphreys P, Jones M, Lane J, Larsson G, Lotan M, Percy A, Pineda M, Skinner S, Syhler B, Thompson S, Weiss B, Witt Engerström I, Downs J. Clinical guidelines for management of bone health in Rett syndrome based on expert consensus and available evidence. PLoS One. 2016;11:e0146824. PubMed PMID: 26849438.

Kankirawatana P, Leonard H, Ellaway C, Scurlock J, Mansour A, Makris CM, Dure LS 4th, Friez M, Lane J, Kiraly-Borri C, Fabian V, Davis M, Jackson J, Christodoulou J, Kaufmann WE, Ravine D, Percy AK. Early progressive encephalopathy in boys and MECP2 mutations. Neurology. 2006;67:164–6. PubMed PMID: 16832102.

Kaufmann WE, Jarrar MH, Wang JS, Lee YJ, Reddy S, Bibat G, Naidu S. Histone modifications in Rett syndrome lymphocytes: a preliminary evaluation. Brain Dev. 2005;27:331–9. PubMed PMID: 16023547.

Klauck SM, Lindsay S, Beyer KS, Splitt M, Burn J, Poustka A. A mutation hot spot for nonspecific X-linked mental retardation in the MECP2 gene causes the PPM-X syndrome. Am J Hum Genet. 2002;70:1034–7. PubMed PMID: 11885030.

Kortüm F, Das S, Flindt M, Morris-Rosendahl DJ, Stefanova I, Goldstein A, Horn D, Klopocki E, Kluger G, Martin P, Rauch A, Roumer A, Saitta S, Walsh LE, Wieczorek D, Uyanik G, Kutsche K, Dobyns WB. The core FOXG1 syndrome phenotype consists of postnatal microcephaly, severe mental retardation, absent language, dyskinesia, and corpus callosum hypogenesis. J Med Genet. 2011;48:396–406. PubMed PMID: 21441262.

Kriaucionis S, Bird A. The major form of MeCP2 has a novel N-terminus generated by alternative splicing. Nucleic Acids Res. 2004;32:1818–23. PubMed PMID: 15034150.

Kudo S, Nomura Y, Segawa M, Fujita N, Nakao M, Dragich J, Schanen C, Tamura M. Functional analyses of MeCP2 mutations associated with Rett syndrome using transient expression systems. Brain Dev. 2001;23:S165–73. PubMed PMID: 11738866.

Kudo S, Nomura Y, Segawa M, Fujita N, Nakao M, Hammer S, Schanen C, Terai I, Tamura M. Functional characterisation of MeCP2 mutations found in male patients with X linked mental retardation. J Med Genet. 2002;39:132–6. PubMed PMID: 11836365.

Kudo S, Nomura Y, Segawa M, Fujita N, Nakao M, Schanen C, Tamura M. Heterogeneity in residual function of MeCP2 carrying missense mutations in the methyl CpG binding domain. J Med Genet. 2003;40:487–93. PubMed PMID: 12843318.

Lambert S, Maystadt I, Boulanger S, Vrielynck P, Destrée A, Lederer D, Moortgat S. Expanding phenotype of p.Ala140Val mutation in MECP2 in a 4 generation family with X-linked intellectual disability and spasticity. Eur J Med Genet. 2016;59:522–5. PubMed PMID: 27465203.

Laurvick CL, de Klerk N, Bower C, Christodoulou J, Ravine D, Ellaway C, Williamson S, Leonard H. Rett syndrome in Australia: a review of the epidemiology. J Pediatr. 2006;148:347–52. PubMed PMID: 16615965.

Leonard H, Colvin L, Christodoulou J, Schiavello T, Williamson S, Davis M, Ravine D, Fyfe S, de Klerk N, Matsuishi T, Kondo I, Clarke A, Hackwell S, Yamashita Y. Patients with the R133C mutation: is their phenotype different from patients with Rett syndrome with other mutations? J Med Genet. 2003;40:e52. PubMed PMID: 12746406.

Leonard H, Ravikumara M, Baikie G, Naseem N, Ellaway C, Percy A, Abraham S, Geerts S, Lane J, Jones M, Bathgate K, Downs J, et al. Assessment and management of nutrition and growth in Rett syndrome. J Pediatr Gastroenterol Nutr. 2013;57:451–60. PubMed PMID: 24084372.

Leonard H, Silberstein J, Falk R, Houwink-Manville I, Ellaway C, Raffaele LS, Engerstrom IW, Schanen C. Occurrence of Rett syndrome in boys. J Child Neurol. 2001;16:333–8. PubMed PMID: 11392517.

Lindsay S, Splitt M, Edney S, Berney TP, Knight SJ, Davies KE, O'Brien O, Gale M, Burn J. PPM-X: a new X-linked mental retardation syndrome with psychosis, pyramidal signs, and macroorchidism maps to Xq28. Am J Hum Genet. 1996;58:1120–6. PubMed PMID: 8651288.

Lubs H, Abidi F, Bier JA, Abuelo D, Ouzts L, Voeller K, Fennell E, Stevenson RE, Schwartz CE, Arena F. XLMR syndrome characterized by multiple respiratory infections, hypertelorism, severe CNS deterioration and early death localizes to distal Xq28. Am J Med Genet. 1999;85:243–8. PubMed PMID: 10398236.

Lugtenberg D, Kleefstra T, Oudakker AR, Nillesen WM, Yntema HG, Tzschach A, Raynaud M, Rating D, Journel H, Chelly J, Goizet C, Lacombe D, Pedespan JM, Echenne B, Tariverdian G, O'Rourke D, King MD, Green A, van Kogelenberg M, Van Esch H, Gecz J, Hamel BC, van Bokhoven H, de Brouwer AP. Structural variation in Xq28: MECP2 duplications in 1% of patients with unexplained XLMR and in 2% of male patients with severe encephalopathy. Eur J Hum Genet. 2009;17:444–53. PubMed PMID: 18985075.

Makedonski K, Abuhatzira L, Kaufman Y, Razin A, Shemer R. MeCP2 deficiency in Rett syndrome causes epigenetic aberrations at the PWS/AS imprinting center that affects UBE3A expression. Hum Mol Genet. 2005;14:1049–58. PubMed PMID: 15757975.

Mari F, Caselli R, Russo S, Cogliati F, Ariani F, Longo I, Bruttini M, Meloni I, Pescucci C, Schurfeld K, Toti P, Tassini M, Larizza L, Hayek G, Zappella M, Renieri A. Germline mosaicism in Rett syndrome identified by prenatal diagnosis. Clin Genet. 2005;67:258–60. PubMed PMID: 15691364.

Meins M, Lehmann J, Gerresheim F, Herchenbach J, Hagedorn M, Hameister K, Epplen JT. Submicroscopic duplication in Xq28 causes increased expression of the MECP2 gene in a boy with severe mental retardation and features of Rett syndrome. J Med Genet. 2005;42:e12. PubMed PMID: 15689435.

Meloni I, Bruttini M, Longo I, Mari F, Rizzolio F, D'Adamo P, Denvriendt K, Fryns JP, Toniolo D, Renieri A. A mutation in the rett syndrome gene, MECP2, causes X-linked mental retardation and progressive spasticity in males. Am J Hum Genet. 2000;67:982–5. PubMed PMID: 10986043.

Miltenberger-Miltenyi G, Laccone F. Mutations and polymorphisms in the human methyl CpG-binding protein MECP2. Hum Mutat. 2003;22:107–15. PubMed PMID: 12872250.

Mnatzakanian GN, Lohi H, Munteanu I, Alfred SE, Yamada T, MacLeod PJ, Jones JR, Scherer SW, Schanen NC, Friez MJ, Vincent JB, Minassian BA. A previously unidentified MECP2 open reading frame defines a new protein isoform relevant to Rett syndrome. Nat Genet. 2004;36:339–41. PubMed PMID: 15034579.

Moog U, Smeets EE, van Roozendaal KE, Schoenmakers S, Herbergs J, Schoonbrood-Lenssen AM, Schrander-Stumpel CT. Neurodevelopmental disorders in males related to the gene causing Rett syndrome in females (MECP2). Eur J Paediatr Neurol. 2003;7:5–12. PubMed PMID: 12615169.

Neul JL, Kaufmann WE, Glaze DG, Christodoulou J, Clarke AJ, Bahi-Buisson N, Leonard H, Bailey ME, Schanen NC, Zappella M, Renieri A, Huppke P, Percy AK, et al. Rett syndrome: revised diagnostic criteria and nomenclature. Ann Neurol. 2010;68:944–50. PubMed PMID: 21154482.

Orrico A, Lam C, Galli L, Dotti MT, Hayek G, Tong SF, Poon PM, Zappella M, Federico A, Sorrentino V. MECP2 mutation in male patients with non-specific X-linked mental retardation. FEBS Lett. 2000;481:285–8. PubMed PMID: 11007980.

Pan H, Li MR, Nelson P, Bao XH, Wu XR, Yu S. Large deletions of the MECP2 gene in Chinese patients with classical Rett syndrome. Clin Genet. 2006;70:418–9. PubMed PMID: 17026625.

Philippe C, Villard L, De Roux N, Raynaud M, Bonnefond JP, Pasquier L, Lesca G, Mancini J, Jonveaux P, Moncla A, Chelly J, Bienvenu T. Spectrum and distribution of MECP2 mutations in 424 Rett syndrome patients: a molecular update. Eur J Med Genet. 2006;49:9–18. PubMed PMID: 16473305.

Poirier K, Francis F, Hamel B, Moraine C, Fryns JP, Ropers HH, Chelly J, Bienvenu T. Mutations in exon 1 of MECP2B are not a common cause of X-linked mental retardation in males. Eur J Hum Genet. 2005;13:523–4. PubMed PMID: 15770224.

Psoni S, Sofocleous C, Traeger-Synodinos J, Kitsiou-Tzeli S, Kanavakis E, Fryssira-Kanioura H. Phenotypic and genotypic variability in four males with MECP2 gene sequence aberrations including a novel deletion. Pediatr Res. 2010;67:551–6. PubMed PMID: 20098342.

Ramocki MB, Peters SU, Tavyev YJ, Zhang F, Carvalho CM, Schaaf CP, Richman R, Fang P, Glaze DG, Lupski JR, Zoghbi HY. Autism and other neuropsychiatric symptoms are prevalent in individuals with MeCP2 duplication syndrome. Ann Neurol. 2009;66:771–82. PubMed PMID: 20035514.

Ravn K, Nielsen JB, Skjeldal OH, Kerr A, Hulten M, Schwartz M. Large genomic rearrangements in MECP2. Hum Mutat. 2005;25:324. PubMed PMID: 15712379.

Sarajlija A, Kisic-Tepavcevic D, Nikolic Z, Savic Pavicevic D, Obradovic S, Djuric M, Pekmezovic T. Epidemiology of Rett syndrome in Serbia: prevalence, incidence and survival. Neuroepidemiology. 2015;44:1–5. PubMed PMID: 25571926.

Saunders CJ, Minassian BE, Chow EW, Zhao W, Vincent JB. Novel exon 1 mutations in MECP2 implicate isoform MeCP2_e1 in classical Rett syndrome. Am J Med Genet A. 2009;149A:1019–23. PubMed PMID: 19365833.

Saxena A, de Lagarde D, Leonard H, Williamson SL, Vasudevan V, Christodoulou J, Thompson E, MacLeod P, Ravine D. Lost in translation: translational interference from a recurrent mutation in exon 1 of MECP2. J Med Genet. 2006;43:470–7. PubMed PMID: 16155192.

Schanen C, Houwink EJ, Dorrani N, Lane J, Everett R, Feng A, Cantor RM, Percy A. Phenotypic manifestations of MECP2 mutations in classical and atypical Rett syndrome. Am J Med Genet A. 2004;126A:129–40. PubMed PMID: 15057977.

Schanen NC, Kurczynski TW, Brunelle D, Woodcock MM, Dure LS 4th, Percy AK. Neonatal encephalopathy in two boys in families with recurrent Rett syndrome. J Child Neurol. 1998;13:229–31. PubMed PMID: 9620015.

Schönewolf-Greulich B, Tejada MI, Stephens K, Hadzsiev K, Gauthier J, Brøndum-Nielsen K, Pfundt R, Ravn K, Maortua H, Gener B, Martínez-Bouzas C, Piton A, Rouleau G, Clayton-Smith J, Kleefstra T, Bisgaard AM, Tümer Z. The MECP2 variant c.925C>T (p.Arg309Trp) causes intellectual disability in both males and females without classic features of Rett syndrome. Clin Genet. 2016;89:733–8. PubMed PMID: 26936630.

Schüle B, Armstrong DD, Vogel H, Oviedo A, Francke U. Severe congenital encephalopathy caused by MECP2 null mutations in males: central hypoxia and reduced neuronal dendritic structure. Clin Genet. 2008;74:116–26. PubMed PMID: 18477000.

Schwartzman JS, Bernardino A, Nishimura A, Gomes RR, Zatz M. Rett syndrome in a boy with a 47,XXY karyotype confirmed by a rare mutation in the MECP2 gene. Neuropediatrics. 2001;32:162–4. PubMed PMID: 11521215.

Sheikh TI, Ausió J, Faghfoury H, Silver J, Lane JB, Eubanks JH, MacLeod P, Percy AK, Vincent JB. From function to phenotype: impaired DNA binding and clustering correlates with clinical severity in males with missense mutations in MECP2. Sci Rep. 2016;6:38590. PubMed PMID: 27929079.

Sheikh TI, de Paz AM, Akhtar S, Ausió J, Vincent JB. MeCP2_E1 N-terminal modifications affect its degradation rate and are disrupted by the Ala2Val Rett mutation. Hum Mol Genet. 2017;26:4132–41. PubMed PMID: 28973632.

Stallworth JL, Dy ME, Buchanan CB, Chen CF, Scott AE, Glaze DG, Lane JB, Lieberman DN, Oberman LM, Skinner SA, Tierney AE, Cutter GR, Percy AK, Neul JL, Kaufmann WE. Hand stereotypies: lessons from the Rett Syndrome Natural History Study. Neurology. 2019;92:e2594–603. PubMed PMID: 31053667.

Topçu M, Akyerli C, Sayi A, Toruner GA, Kocoglu SR, Cimbis M, Ozcelik T. Somatic mosaicism for a MECP2 mutation associated with classic Rett syndrome in a boy. Eur J Hum Genet. 2002;10:77–81. PubMed PMID: 11896459.

Van Esch H, Bauters M, Ignatius J, Jansen M, Raynaud M, Hollanders K, Lugtenberg D, Bienvenu T, Jensen LR, Gecz J, Moraine C, Marynen P, Fryns JP, Froyen G. Duplication of the MECP2 region is a frequent cause of severe mental retardation and progressive neurological symptoms in males. Am J Hum Genet. 2005;77:442–53. PubMed PMID: 16080119.

Venâncio M, Santos M, Pereira SA, Maciel P, Saraiva JM. An explanation for another familial case of Rett syndrome: maternal germline mosaicism. Eur J Hum Genet. 2007;15:902–4. PubMed PMID: 17440498.

Venkateswaran S, McMillan HJ, Doja A, Humphreys P. Adolescent onset cognitive regression and neuropsychiatric symptoms associated with the A140V MECP2 mutation. Dev Med Child Neurol. 2014;56:91–4. PubMed PMID: 24328834.

Villard L, Kpebe A, Cardoso C, Chelly PJ, Tardieu PM, Fontes M. Two affected boys in a Rett syndrome family: clinical and molecular findings. Neurology. 2000;55:1188–93. PubMed PMID: 11071498.

Wan M, Lee SS, Zhang X, Houwink-Manville I, Song HR, Amir RE, Budden S, Naidu S, Pereira JL, Lo IF, Zoghbi HY, Schanen NC, Francke U. Rett syndrome and beyond: recurrent spontaneous and familial MECP2 mutations at CpG hotspots. Am J Hum Genet. 1999;65:1520–9. PubMed PMID: 10577905.

Weaving LS, Williamson SL, Bennetts B, Davis M, Ellaway CJ, Leonard H, Thong MK, Delatycki M, Thompson EM, Laing N, Christodoulou J. Effects of MECP2 mutation type, location and X-inactivation in modulating Rett syndrome phenotype. Am J Med Genet A. 2003;118A:103–14. PubMed PMID: 12655490.

Winnepenninckx B, Errijgers V, Hayez-Delatte F, Reyniers E, Frank Kooy R. Identification of a family with nonspecific mental retardation (MRX79) with the A140V mutation in the MECP2 gene: is there a need for routine screening? Hum Mutat. 2002;20:249–52. PubMed PMID: 12325019.

Young JI, Hong EP, Castle JC, Crespo-Barreto J, Bowman AB, Rose MF, Kang D, Richman R, Johnson JM, Berget S, Zoghbi HY. Regulation of RNA splicing by the methylation-dependent transcriptional repressor methyl-CpG binding protein 2. Proc Natl Acad Sci USA. 2005;102:17551–8. PubMed PMID: 16251272.

Zahorakova D, Rosipal R, Hadac J, Zumrova A, Bzduch V, Misovicova N, Baxova A, Zeman J, Martasek P. Mutation analysis of the MECP2 gene in patients of Slavic origin with Rett syndrome: novel mutations and polymorphisms. J Hum Genet. 2007;52:342–8. PubMed PMID: 17387578.

Zeev BB, Yaron Y, Schanen NC, Wolf H, Brandt N, Ginot N, Shomrat R, Orr-Urtreger A. Rett syndrome: clinical manifestations in males with MECP2 mutations. J Child Neurol. 2002;17:20–4. PubMed PMID: 11913564.

Zhang Q, Yang X, Wang J, Li J, Wu Q, Wen Y, Zhao Y, Zhang X, Yao H, Wu X, Yu S, Wei L, Bao X. Genomic mosaicism in the pathogenesis and inheritance of a Rett syndrome cohort. Genet Med. 2019;21:1330–8. PubMed PMID: 30405208.

Chapter Notes

Author History

Vicky L Brandt; Baylor College of Medicine (2000-2004)
John Christodoulou, MBBS, PhD, FRACP, FRCPA, FHGSA (2006-present)
Gladys Ho, MSc; Children's Hospital at Westmead, Sydney (2009-2019)
Simranpreet Kaur, MSci, MPhil (2019-present)
Huda Y Zoghbi, MD; Baylor College of Medicine (2004-2006)

Revision History

- 19 September 2019 (bp) Comprehensive update posted live
- 28 June 2012 (me) Comprehensive update posted live
- 2 April 2009 (me) Comprehensive update posted live
- 25 January 2008 (cd) Revision: *MECP2* duplication syndrome added to Genetically Related Disorders
- 15 August 2006 (me) Comprehensive update posted live
- 11 February 2004 (me) Comprehensive update posted live
- 3 October 2001 (me) Review posted live
- September 2000 (vb) Original submission

License